REMARKS

Claims 21-24, 28-38, 40-42, 46, 48-54, 56, 57, 63-66, and 68-75 were pending in the application. Claims 38, 40-42, 46, 48-54, 56, 57, 63, 66, 71-73, 42 are cancelled by this amendment without prejudice or disclaimer. Claims 21 and 22 have been amended for clarity. New claims 76 and 77 have been added and are directed to certain subject matter deleted from claims 21 and 22. Support for the amended and new claims is found *inter alia* in the specification and claims as originally filed. For example, support for the amendments to claims 21 and 22 is found in original claim 1. No new matter is added by these amendments. Upon entry of this amendment, claims 21, 22-24, 28-37, 64, 65, 68-70, 74, and 75 will be pending.

The claimed invention is directed to injectable (volume weighted mean particle size up to 3 microns) aqueous terminally steam sterilized compositions of a particulate suspension of a water insoluble or poorly soluble biologically active substance in which the particles are stabilized with one or more phospholipids and a water soluble polyhydroxy thermoprotecting agent, *e.g.*, trehalose, lactose, dextrose, sorbitol, dextran, mannitol (emphasis added).

The invention provides a terminally steam sterilized (autoclaved) aqueous microsuspension of a phospholipid-stabilized active, which maintains a micron to submicron particle size and is devoid of surfactants that require elevation of their cloud point temperature by addition of a cloud point modifier and those that coagulate upon steam sterilization (emphasis added).

Rejections under 35 U.S.C. § 103

Claims 21-24, 28-38, 40-42, 46, 48-54, 56, 57, 63-66, and 68-75 remain rejected as unpatentable over US 5,858,410 (filed Nov. 9, 1995, "Muller") and US 5,739,152 (filed Nov. 3, 1994, "Anderson"). The rejections are traversed as applied to amended claims 21 and 22, which are the only remaining independent claims.

Claims 21 and 22 have been amended to emphasize that the claimed subject matter is directed to injectable (*i.e.*, having a volume weighted mean particle size up to 3 microns) aqueous terminally steam sterilized compositions of a particulate suspension of a water insoluble or poorly soluble biologically active substance in which the particles are stabilized with one or

more phospholipids and a water soluble polyhydroxy thermoprotecting agent, *e.g.*, trehalose, lactose, dextrose, sorbitol, dextran, mannitol (emphasis added).

Muller describes the use of cavitation (*e.g.*, by high-pressure homogenization) for producing nanosuspensions of solid poorly water soluble drug particles. *See* Muller at col. 5, lines 3-26. Muller notes that, although this technique had been used for producing fine dispersions of oils in the context of making fat emulsions for parenteral feeding, it was believed unsuitable for use with solids. *Id.* Muller describes success in forming nanosuspensions of poorly water soluble drugs using this technique. Since the compositions are intended for intravenous delivery, Muller also describes their sterilizability, *inter alia*, by steam sterilization (autoclaving). In particular, Muller describes the influence of surfactants on the physical stability of the steam sterilized compositions, *i.e.*, their stability against particle size growth. *See* Muller at col. 7 line 21 to col. 8 line 26. Muller demonstrates in Example 12 the unpredictability of the effects that any particular surfactant will have on the physical stability of the nanosuspensions. Example 12 compares the stability of the suspensions following steam sterilization as a function of the surfactant concentration using Tween 80 as the surfactant. *See* Muller at col. 16, lines 38-67 (Example 12 and Figure 17). The results demonstrate that the compositions were stable with an amount of Tween 80 that was "in the range of the concentration for reaching the plateau of the adsorption isotherms" or slightly below it. Muller at col. 8, lines 19-24. This was unexpected because, on the basis of theoretical considerations, one would have expected stabilization to occur with the surfactant at amounts "significantly above the concentration [needed] to reach the plateau of the adsorptions isotherms". Muller at col. 7, lines 30-34 (emphasis added). Muller does not describe or exemplify a nanosuspension stabilized against particle size growth during terminal steam sterilization other than those containing Tween 80 and mannitol. *See* Muller in Examples 10, 12 and Figures 13, 17. Muller exemplifies a phospholipid-containing nanosuspension in Examples 14-16. But these compositions are not subjected to steam sterilization and they do not contain a water soluble polyhydroxy thermoprotecting agent, as required by claims 21 and 22. Nor is there any rationale provided by the Examiner or any suggestion in Muller that would direct the skilled person to combine a water soluble polyhydroxy thermoprotecting agent with a phospholipid-containing particulate suspension of an active agent, as claimed.

Andersson describes a phospholipid-containing pharmaceutical emulsion that is stable after steam sterilization (autoclaving). *See e.g.*, Andersson at col. 6, lines 62-67 (emphasis added). But the oil-in-water emulsions described by Andersson are categorically different from the particulate suspensions described by Muller. The emulsions described by Andersson do not comprise particles of the active. Instead, the active is dissolved in the lipid phase. *See e.g.*, Andersson at col. 6, lines 15-16. Accordingly, such emulsions are not subject to the same physical instability following steam sterilization as the particulate suspensions of Muller. Thus, the skilled person would not expect success in obtaining a phospholipid-containing suspension that is stable against particle size growth upon steam sterilization based on the description of phospholipid-containing emulsions described by Andersson. Accordingly, the combination of Andersson does not remedy the skilled person's lack of a reason to modify the compositions of Muller as urged by the Examiner (to combine a water soluble polyhydroxy thermoprotecting agent with a phospholipid-containing nanosuspension) or her lack of a reasonbable expectation of success in doing so (based on the demonstrated lack of predictability in Example 12).

It is noted that, in the Examiner's view, Muller describes the use of a phospholipid in combination with a water soluble polyhydroxy thermoprotecting agent, *e.g.*, trehalose, lactose, dextrose, sorbitol, dextran, or mannitol. Office Action at p. 4. The Examiner points to claims 1-22 of Muller in support of this position. *See* Final Office action mailed July 6, 2011, at p. 3. Applicants' position is that, even if the skilled person were to consider combining a phospholipid with a thermoprotecting agent, she would not have had a reasonable expectation of success based upon the combination of Muller and Andersson. This is because Muller clearly demonstrates in Example 12 the unpredictability of added surfactants on the stability of the nanosuspension against particle size growth upon steam sterilization, as discussed above. The fact that Andersson describes phospholipid containing oil-in-water emulsions (in which the active is dissolved in the lipid layer) that are stable after autoclaving does nothing to render predictable the stability of the claimed phospholipid-containing suspensions. This is because, as discussed above, an oil-in-water emulsion is a categorically different composition from a particulate suspension and it is not subject to same deleterious particle size growth as a particulate suspension.

Moreover, and further to clarify the record, Applicants point out that the claims of Muller do not in fact read on a composition having a phospholipid in combination with trehalose or manntiol, as urged by the Examiner. Both "lecithins" and "phospholipids" are recited in claim 14 of Muller among the list of suitable "dispersion-stabilizing substances". Claim 14 depends from claim 12, which in turn depends directly from claim 1. Trehalose and mannitol are recited in claim 22 of Muller as among the compounds which may further comprise the composition of claim 19, which depends directly from claim 1. Thus, while the claims of Muller read on a composition comprising either a phospholipid (claim 14) or trehalose or mannitol (claim 22), the claims do not read on a composition containing both. Indeed, this failure of Muller to describe the claimed combination supports Applicants' position because it further illustrates that Muller failed to recognize the use of these compounds as thermoprotecting agents to stabilize a phospholipid containing suspension against particle size growth following steam sterilization. Indeed, there is no teaching or suggestion in the combination of Muller and Andersson to point the skilled person to the claimed combination, precisely because the stabilizing effects of the claimed water soluble polyhydroxy thermoprotecting agents was not recognized in the prior art.

In summary, the combination of Muller and Andersson fails to support a *prima facie* case of obviousness against the invention of claims 21 and 22 because the combination neither describes nor suggests the claimed injectable aqueous terminally steam sterilized compositions of a particulate suspension of a phospholipid-stabilized active and a polyhydroxy thermoprotecting agent, as claimed. Nor would the skilled person expect success in modifying Muller as urged by the Examiner to add a polyhydroxy thermoprotecting agent to a particulate suspension of a phospholipid-stabilized active because Muller demonstrates the unpredictability associated with the addition of surfactant stabilizers to its nanosuspensions, as discussed above. Reconsideration and withdrawal of the rejection of claims 21 and 22, and their dependent claims, under 35 U.S.C. § 103(a) is respectfully requested.

Claims 64 and 65

Dependent claims 64 and 65 are treated separately here because the combination of Muller and Andersson fails to describe or suggest an injectable aqueous terminally steam sterilized composition of a particulate suspension of a water insoluble or poorly soluble biologically active substance which consists of the biologically active substance, said one or

more phospholipid surface modifiers, and said polyhydroxy thermoprotecting agent. None of the compositions described in the combination of references consists of the active, a phospholipid, and a polyhydroxy thermoprotecting agent, as claimed. Accordingly, reconsideration and withdrawal of the rejection as applied to claims 64 and 65 is respectfully requested.

Response to Examiner's Remarks

In addition to the remarks above, Applicants respond separately to certain statements made by the Examiner that are not directly addressed above. First, the Examiner characterizes Andersson as describing "autoclaving a dispersion of an active agent under nitrogen to get a composition, which is stable". Office action at p. 3, para. 3 and also at p. 4, para. 4. For point of clarity, autoclaving is not done "under nitrogen". Applicants have amended claims 21 and 22, in part, to clarify that in one embodiment the compositions are supplied under nitrogen in a sealed vial (see new dependent claims 76 and 77). In addition, the Examiner is apparently suggesting that Andersson teaches autoclaving as a means to obtain a stable composition. Office action at p. 4, para. 2 (emphasis added). Andersson states that its oil-in-water emulsions, after autoclaving, were stable. Andersson at col. 6, lines 62-67. Indeed, the successful terminal steam sterilization of phospholipid-stabilized emulsions is noted in Applicants' specification and is not contested. *See* specification at p. 2, para. 2. But Andersson does not teach or suggest autoclaving as a means to obtain a stable composition. And with respect to the claimed particulate suspensions, autoclaving is recognized as introducing undesirable particle size growth, which is a form of physical instability that makes the compositions unsuitable for their intended use as injectable compositons. *See e.g.*, the specification at p. 1-2 (bridging para.); *see also* discussion in Muller at col. 7, lines 30-63.

The Examiner also states that Muller "uses autoclaving as a mean[sic] of sterilization for a microemulsions [sic] having tween 80, and does not address any instability." This statement is inaccurate. First, Muller describes suspensions and not emulsions. As discussed above, the fundamental difference is that the suspensions of Muller contain particles of the active, whereas an emulsion such as that described by Andersson contains the active dissolved in the oil phase. This amounts to fundamentally different compositions which are not analogous with respect to their stability following steam sterilization. Second, Muller does indeed address the instability associated with the addition of Tween 80 to its suspensions, specifically in Example 12 and in

the discussion of same, as noted above in relation to the rejections on Section 103. *See* Muller at col. 8, lines 19-24 and col. 16, lines 38-67.

Applicants submit that the application is in condition for allowance and request an action for the same. No fee is believed due in connection with this paper. However, if any fee is due, please charge the amount of any such fee, or credit any overpayment of same, to Deposit Account 50-0311, Attorney Reference No.: **28069-503001US**.

Respectfully submitted,

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